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A General Theory of Bone Tumors

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Although pathologists attempt to classify tumors into readily separable groups on the basis of morphology and behavior, many tumors do not completely conform to their classification. To classify bone tumors with descriptive fidelity would frequently necessitate multi-hyphenated terms because of "impure" tumors which exhibit the traits of several categories. In clinical practice it is convenient to think of the major bone tumors as falling into ten basic types, and to label individual specimens, according to the concept of "predominant cell type," with that one of the following terms which gives the best approximation.

Chondrosarcoma
"Chondroblastoma" (Codman's tumor)
Osteosarcoma
"Osteoblastoma" (parosteal osteoma)
(juxtacortical sarcoma)
Giant cell tumor (osteoclastoma)
"Osteolytic sarcoma"
(pleomorphic sarcoma)
Fibrosarcoma (medullary)
Reticulum cell sarcoma
Ewing tumor
Multiple myeloma

Underlying these approximations is a range of cell types and organoid patterns common to all of the categories. Furthermore, they all share in a common biochemistry and cytology of matrix formation, and they conform to regional variations in the structure of normal bones and of the skeleton. And when the tumors are analyzed with respect to space, time, and quantity—where, when, and how often they occur—it would appear that they behave in an orderly and predictable manner.

1. *Histology of the Tumors.* Each of these ten types is a distinct clinical, radiologic, and anatomic complex named for a characteristic and predominant cell type that is usually recognized by its products; e.g., osteosarcoma and chondrosarcoma are so named because they produce bone and cartilage respectively. The chondroblastoma of Jaffe (Codman's "epiphyseal chondromatous giant cell tumor") is a relatively mature tumor made up of cells that approach the appearance and behavior of normal chondroblasts. "Osteoblastoma" would be the homologous term for the tumor of osteoblasts called "parosteal osteoma" by Geschickter and Copeland (Jaffe's "juxtacortical osteosarcoma"). Both "blastomas" are slow growing and sufficiently mature in appearance to be mistaken at times for non-neoplastic hyperplasias or reparative patterns.

The large cell for which the giant cell tumor is named shows the same phosphatase

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activity as the osteoclast, is likewise free of phagocytic activity, and may metastasize to the lung in malignant forms of this tumor. Hence, the giant cells are regarded as neoplastic osteoclasts. And because transitional forms between the giant cells and the so-called "stroma cells" are demonstrable, the latter are regarded as mononuclear predecessors of the multinucleated forms.

"Osteolytic sarcoma" is the term used to designate a primary tumor that destroys bone and is made up of extremely pleomorphic cells that generally fail to produce any matrix. Whole bone sections of these tumors have on several occasions shown the characteristic cell types merging into areas typical of malignant and even of benign giant cell tumor; therefore we regard it as an extremely malignant derivative of the giant cell tumor.

All of the fibrosarcomas in our material are medullary in origin; those thought to be periosteal fibrosarcomas generally proved to be primary in the soft tissue adjacent to, but not part of, the bone.

When some 1500 tumors in the Registry of Orthopedic Pathology were classified and analyzed, a very wide range of cell types was noted in each category. For example, within the group of typical chondrosarcomas individual fields were morphologically indistinguishable from osteosarcoma, Codman's tumor, parosteal sarcoma, giant cell tumor, osteolytic sarcoma, fibrosarcoma, reticulum cell sarcoma, Ewing tumor, and even myeloma. A similar range of cell types may be found in every class of tumor; the mononuclear "stroma cells" of giant cell tumors undergoing sarcomatous transformation are quite likely to lay down a chondroid matrix; in reticulum cell sarcomas, collagen, fibrocartilage, and osteoid material may form in condensations of the abundant reticulum.

While the Ewing tumor is usually thought of as monotonous sheets of closely packed, generally round nuclei, with scarcely any visible cytoplasm, Ewing himself illustrated cells with considerable water-clear cytoplasm. When these suggestions of cytoplasmic activity were investigated, we found them to result in extracellular mucoid material which occasionally developed into patches of typical cartilage or into slender spicules of chondro-osteoid material, birefringent in polarized light and occasionally calcified.

Likewise, myeloma cells, in addition to amyloid, Bence-Jones protein, and a lipoprotein associated with anticomplementary Wassermann reactions, were found to produce an abundance of reticulum, patches of mucoid material, and occasional optically active chondro-osteoid bands that sometimes calcify. Furthermore, the appearance of myeloma cells and their reaction to methyl green pyronine are as closely duplicated by the normal osteoblasts of undecalcified embryonic bone as they are by non-neoplastic plasma cells.

Therefore, at least some of the osseous reticulum cell sarcomas, Ewing tumors, and multiple myelomas can produce matrices which are characteristic of skeletal tissue, and such behavior would seem to indicate that they belong among the skeletal neoplasms.

2. *Biochemical and Cytological Background.* The interpretation of these observations is dependent upon the known chemical properties of normal bone matrix. The organic component of both bone and cartilage is made up of a fiber protein of the reticulum-collagen series and a mucoid glycoprotein of the mucopolysaccharide series, with the fiber protein predominant in bone and the glycoprotein predominant in cartilage. The fiber protein has a special configuration of particular amino acids and a characteristic pattern on electron microscopy and on x-ray diffraction. The mucopolysaccharide consists of long chains of cyclical hexose derivatives, with sulfate and amino side radicals. The fiber protein and the polysaccharide can combine stoicheiometrically because of similar periodicity and strategically placed active side radicals to produce a single new substance, osteoid, which is able to calcify after molecular rearrangement and loss of water.

The collagen and polysaccharide are the products of osteoblasts and of chondroblasts. Collagen is probably synthesized from polypeptides and amino acids in a protein-rich tissue fluid by the interface activity of the cell "membrane," and is thus

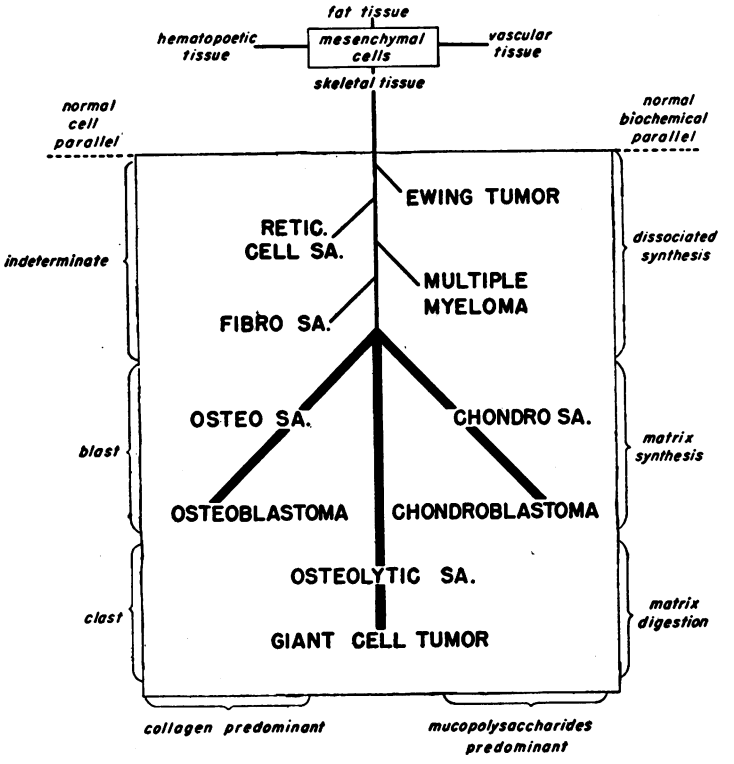

Fig. 1

an extracellular produet. The mucopolysaccharide, on the other hand, appears to be produced within the cytoplasm and is secreted onto the developing collagen. Ordinarily it takes about ten days for osteoblasts to produce calcified bone, but only eight hours for an osteoclast to digest and destroy it enzymatically, a time differential of considerable importance when balancing osteoblastic against osteoclastic activity.

The relationship between osteoblasts and osteoclasts is particularly well displayed in the egg laying cycle of birds; calcium is stored by filling the marrow cavities with bone while the ovum is maturing and is released by clearing out the extra bone for the eggshell when the egg enters the shell sac. When this cycle is telescoped into twenty hours (as in the pigeon) it appears that the osteoblast and the osteoclast are the same cell, since they rapidly change from one morphologic type and function to the other, without intervening cell division. Hence the names given to the cells merely designate varying forms and functions of the same cell.

3. *Interpretation of Relationship of Tumor Types.* When the full range of cell types in each of the ten categories of tumors is considered against this background, a precise form of kinship may be postulated (see diagram), based upon the degree to which each tumor type duplicates the normal organic chemistry of matrix production. The tumors in the upper third represent incomplete patterns of organic synthesis, while those of the middle third regularly produce abundant skeletal matrix. On one side are those tumors of predominantly collagenic structure, and on the other, those of

predominantly glycoprotein makeup. Tumors of the lower third consist of cells which attempt to duplicate osteoclastic activity.

This formulation suggests that abortive attempts at organic synthesis may occur in the Ewing tumor and permit the escape of polypeptides, proteoses, or peptones into the circulation to produce fever, leukocytosis, and elevation of the sedimentation rate—a problem for chromatographic investigation of blood and urine.

Similarly the amyloid, Bence-Jones protein, and other abnormal organic products of multiple myeloma may be complex proteins and lipids resulting from conjugation with the products of abortive mucopolysaccharide synthesis—and polysaccharide studies of blood and urine may clarify such relationships.

Ordinarily the mononuclear cells of the giant cell tumor omit the phase of synthesis and develop directly into multinucleated tumor osteoclasts. But their latent ability to behave as "blast" cells is unmasked by their tendency to produce cartilage in giant cell tumors which are undergoing malignant transformation. The same potential on the part of the mononuclear cells is evidenced by the foci of cartilage to be found in many benign giant cell tumors of the hands and feet, in the rare enchondromatous giant cell tumors of the metaphyses of long bones, and in the epiphyseal chondroblastoma or Codman tumor. Thus, the neoplasms demonstrate the same relationship between "blast" cells and "clast" cells that obtains in normal bone.

4. *Skeletal Metabolic Fields.* Bone is more than a tissue; it is an organ with special and varying functions in different portions not only of the skeleton but also of the separate bones. There is a metabolic gradient within each individual bone as evidenced by variations in thermocouple readings, circulatory rates, capillary and sinusoidal dilatation, mitotic activity, relative proportions of osteoblasts to osteoclasts, rates of organic matrix synthesis, Ca/P ratios, Ca/N ratios, P/N ratios, carbonate/phosphate ratios, rates of exchange of radioactive tracers, and madder feeding, and by the variations of these data with age and with disease. The gradient is a low level in the epiphysis and minimal in the midshaft, while it is high in the metaphyseal regions and maximal in the metaphysis of the more rapidly growing end.

Once the bone has gained sufficient size for the metabolic gradient to be spread out in space, it can be correlated with fields of cell activity (Fig. 2A). In childhood, the epiphysis is only moderately active with a limited and rather precarious blood supply. Not until the growth plate closes does collateral circulation develop from the abundant metaphyseal blood supply. The essentially bloodless growth plate first synthesizes, then resorbs cartilage matrix, simultaneously inducing a narrow zone of intense osteoblastic activity as a result of the phase of cartilage maturation. The subjacent half of the metaphysis (3) is a field of overbalancing osteoclastic activity as primary trabeculae are resorbed and the original cortical silhouette is cut back in remodelling the broad diameter of the growth plate to that of the slender shaft. The diaphyseal half of the metaphysis (4) is a region of compensating preponderance of osteoblastic activity as bone is reconstituted, particularly along the endosteal surface of the cortex. Activity in the diaphysis (5) is largely periosteal in location while endosteal activity and cancellous bone in the marrow cavity disappear by osteoclasis.

During early adolescence, as circumferential growth of the shaft nears completion, the conversion of lamellar bone to Haversian systems begins. After the epiphyseal growth plate closes, the stress-strain cancellous trabeculae (which are present as two independent systems on either side of the plate before closure), are resorbed and simultaneously reconstituted into a single new system of major weight-transmitting trabeculae.

5. *Place of Origin of Tumors.* When the very small and presumably early tumors of each category are analyzed, it becomes apparent that there are preferential sites of origin within each bone. In general, a particular tumor of a given cell type usually arises in that field where the homologous normal cells are most active, as illustrated in Fig. 2B. For example, giant cell tumors,

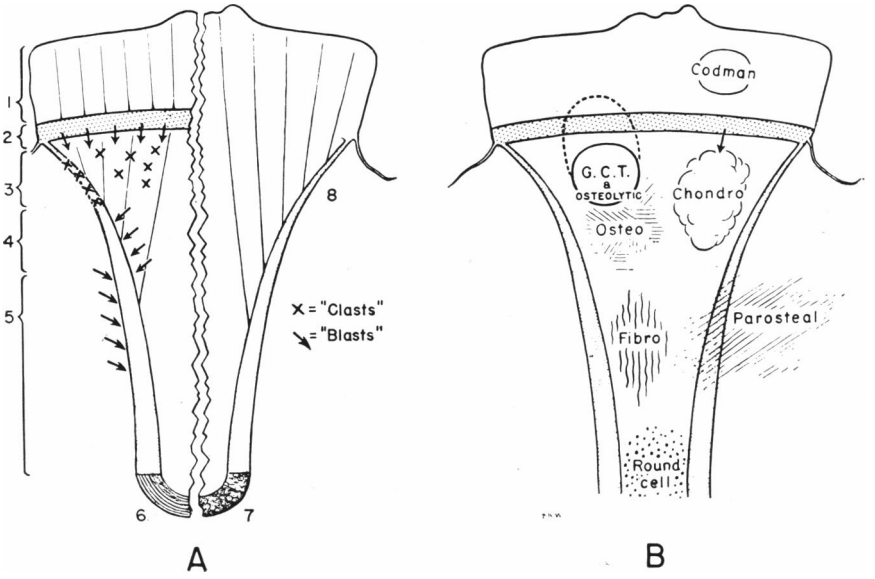

Fig. 2

when small or when seen before the epiphyseal plate closes, are always located in the osteoclastic field of the metaphysis. After the plate disappears they spread, with reconstructive activity, into the epiphysis. As might be anticipated, osteolytic sarcomas have an identical distribution. Fibrosarcomas arise where cancellous bone is disappearing from the medullary cavity. The three round cell sarcomas (myeloma, Ewing's, reticulum cell) develop in the bone-free marrow cavity of the mid-shaft. The parosteal sarcoma arises from the periosteal surface at the junction of the metaphysis and shaft, in the field of predominant periosteal activity. Though usually a tumor of the surface of the cortex, it may occasionally arise within the bone and the internal portion will then appear as a low grade fibrosarcoma. Thus a single tumor may have cellular components which characterize two different fields. Similarly, an occasional sarcoma of adolescence may present as a "double" tumor, appearing as a giant cell tumor in the metaphysis and as an osteosarcoma where it extends into the shaft of the bone.

These regional variations suggest that the character of the tumor may be determined by the metabolic field in which it arises. Such speculations are encouraged by the striking change in cellular make-up of many tumors after they break out of the bone into the soft tissues—as if escaping the control of local field influences. A further suggestion comes from the variation of tumor patterns in different portions of the skeleton. The metabolic gradient of the bones of each limb drops as one progresses distally, and enchondromas, for example, show a parallel decreasing incidence of sarcomatous transformation. (In this respect, the Codman tumor in long bones behaves as if the epiphyseal metabolic level approximated that of the phalanges.)

6. *Time of Origin of Tumors.* The three forms of round cell sarcomas arise in the same general location but in different age groups: childhood-adolescence for Ewing tumor, adulthood for reticulum cell sarcoma, and middle and old age for myeloma. Borderline tumors appear in the third and fourth decade; it may be that the changing metabolic activity of bone with increasing

age may influence the character of the cells comprising the tumor.

Apart from the three round cell tumors, the majority of bone tumors develop in late adolescence—the 15 to 25 year age-range. This is the time of the last growth spurt and maximal reconstructive activity of both cortical and cancellous bone, and it is the period when the various tumors are seen in their most characteristic form. Giant cell tumors, osteosarcomas, and chondrosarcomas predominate (and, if one avoids hyphenated terms, naming the tumors for the quantitatively predominant component, chondrosarcomas are more common them osteosarcomas).

The highly malignant bone tumors of childhood show extensive areas of undifferentiated round cells, so that the osteosarcomas in part resemble Ewing tumors. In mid-adult life, however, the same neoplasms tend to be much slower growing and more mature in appearance. In the fourth decade the usual polyhedral mononuclear "stroma cells" of the giant cell tumor frequently assume spindle patterns to look like fibroblasts, or fill with fat to appear as xanthoma cells. Parosteal sarcomas ("osteoblastoma") and fibrosarcomas, with their notably better prognosis, are largely tumors of this period. Furthermore, there are some periosteal chondrosarcomas of the shaft and a group of osteosarcomas of the midshaft of major long bones that develop in the fourth decade, which are very slow growing and well differentiated, and approximate in prognosis the parosteal sarcoma and fibrosarcoma.

7. *Quantitative Factors in Tumor Incidence.* Although the majority of bone tumors develop during the period of maximal bone reconstruction, it is important also to recall that most of them occur in the longest bones (humerus, tibia and femur) which show the most growth and reconstruction. Furthermore, the larger number occur in that end of each of these bones where growth is greatest (shoulder and knee regions). This suggests a relationship between the number of tumors and the amount of cell activity, a relationship implicit in evidence of an antecedent benign fibrous lesion in 25 per cent of the fibrosarcomas, and in the incidence of chondrosarcomas developing from enchondromas and osteochondromas. The propensity for excessive cellular proliferation to progress to neoplasia is further suggested by the occasional development of bone sarcomas in the actively proliferating margin of a bone infarct, an old osteomyelitic scar, or an old unresolved callus. Recently there has been a growing suspicion that pregnancy may enhance the activity of some bone tumors as might be expected from the additive effect of growth hormone, estrogens, and androgens on osteoblastic activity. Von Recklinghausen's generalized osteitis fibrosa cystica may be associated with true giant cell tumors as well as with the brown tumor of hyperparathyroidism. Finally, Paget's disease is notorious for its high incidence of osteosarcomas and giant cell tumors, and occasionally a peculiar double tumor of both osteoblasts and osteoclasts may be seen.

The underlying common factor would seem to be that diseases characterized by prolonged periods of excessive cell activity carry an increased hazard of neoplastic transformation of those cells.

Summary

Thus, an analysis of where, when, and how often bone tumors occur indicates that these neoplasms are not completely autonomous but are subject to the laws of field behavior of normal bone, which they may caricature, but cannot wholly escape.

The various categories of tumors represent abortive attempts at, or varying degrees of success in recapitulating the organic chemistry of production and destruction of skeletal matrices by the cytoplasmic activity of the cells.

The appearance of a particular tumor seems to be the result of the influence of the field forces upon the neoplastic cells and is manifested by a characteristic cytoplasmic activity which defines the tumor. Thus, the broad aspects of the biologic behavior of bone tumors are reflected in their morphology, and, conversely, their biology may be inferred from a detailed study of their morphology.

DISCUSSION

HENRY L. JAFFE: Dr. Johnson has conveyed to us, very interestingly, his conception of the bone tumors. How he can derive them all from the same basic cell and at the same time recognize that there are clinico-anatomic differences between the various bone tumor entities is the task of his theory to explain. In the first place, he lays great stress upon the fact that, along with the predominant tissue pattern presented by one of the given tumor entities, a specific lesion may show some tissue fields suggesting one or a number of the other clinico-anatomic tumor types. However, he overemphasizes this so-called histologic overlapping of the tissue patterns in the various tumor types, and, furthermore, he fails to note that, in a particular bone tumor, one may encounter tissue elements which are not the product of the actual tumor cells of the lesion at all. Nevertheless, Dr. Johnson is not diverted by this idea of overlapping tissue patterns when faced with the question of classification and of diagnosis directed toward treatment. He recognizes, as do all of us who deal with these matters, that, in applying a diagnosis to a particular tumor, one is guided by the dominant histologic tissue pattern as revealed by microscopic examination of tissue from many different areas of the tumor. It would be difficult to overemphasize, also, that one cannot have an adequate understanding of any particular bone tumor without an adequate understanding of its x-ray picture as a reflection of the gross anatomy of the lesion.

To me, it seems that in the practical approach to bone tumor classification and diagnosis, one must conceive of the different tumors as clinico-pathologic entities toward whose delimitation age and sex distribution, localization, roentgenographic pattern, and dominant histologic pattern all contribute more or less. However, the presentation tonight relates to a general theory of the bone tumors. This theory is based upon the idea that all the different types of tumors originate from a single type of basic cell and that the differences which the tumors eventually present represent merely differences in the degree to which the cell has come to approximate full functional capacity. The corollary of this idea is that the only justification for different names for the different bone tumor entities lies in a difference in clinical behavior. I admire the broad scope of Dr. Johnson's thought on this whole question. But it seems to me that this attempt to reduce the bone tumor problem to the idea of a basic cell played upon by the forces of growth and metabolism obliterates useful distinctions in its attempt to create unity.

Dr. Johnson gave us a clear and vivid summary of protein chemistry as it applies to bone formation, and a dynamic picture of the activity of the osteoblasts and chondroblasts in laying down bone and cartilage matrix. He also pointed up the metabolic interchange that goes on in the bones in general, and in various specific sites in individual bones. I am afraid, however, that all this does not help us as much as he thinks it might in the understanding of bone tumors. The trouble is that he bases much of his argument upon the idea of a close analogy between the physiologic activity and behavior of bone as tissue on the one hand, and the behavior of the tumor tissue of a tumor in bone on the other. Actually, many of the tumors which he forces into a unit on this basis are of fundamentally different natures. This is true, for instance, of multiple myeloma on the one hand, and osteogenic sarcoma and chondrosarcoma on the other. Nevertheless, it is always good to be made to see so vast a subject again as a whole. And this Dr. Johnson has done for us.

FRED W. STEWART: I did not intend to discuss this paper. I spent a week in Washington at the Institute in December, and talked this over with Dr. Johnson and saw some of his material, and I think I was rather more impressed than Dr. Jaffe seems to have been. I feel in fact very sympathetic with his point of view, and I must also say I do not think he has made the effort to destroy or render useless the various existing clinical-pathologic distinctions. He admits their validity.

LENT C. JOHNSON: I wish to thank Dr. Jaffe and Dr. Stewart for their remarks.

In reply to Dr. Jaffe, may I emphasize that statements or implications as to the cell of origin for any of these tumors were carefully avoided. In fact, it was specifically stated that the cells were identified only by their products, that is, descriptively. The cell of origin, like paternity, is often a matter of faith, while the descriptive designation of a cell need not involve commitments regarding its past or its future. This attitude is necessary when within a single slide of the whole tumor from a uterus one can find a leiomyoma undergoing sarcomatous transformation to a myosarcoma and then extensive metaplasia to produce bone. When the bulk of such a tumor is composed of bone, it is descriptively an osteosarcoma, but histogenetically, metaplasia of a myosarcoma. Only the accident of a fortunate section established an unexpected cell of origin. Since this accident seldom occurs in bone tumor, or in tumor slides in general, ideas of cell of origin are still largely a matter of inference and faith. The table demonstrating the relationship between the tumors is not a table of derivation from a cell of origin but of functional and chemical kinship, irrespective of cell of origin.

Dr. Jaffe has properly warned against mistaking tissue elements in a tumor for the actual products of the tumor cells. In all the illustrations that I have shown, a critical selection was made to demonstrate only those matrices that meet the criteria of production by the specific neoplastic cells.

I am certainly in complete agreement with Dr. Jaffe's statement that tumor diagnosis depends on the dominant histologic pattern and that x-ray and clinical correlations are necessary. However, our object this evening was to consider the possible meaning of the subdominant or minor patterns that are also to be found in many tumors. The situation is analogous to the circumstances in the physical sciences after the formulation of the laws governing the behavior of gases in a room such as this. Later studies demonstrated that these laws did not adequately account for the behavior of gases at extremes of temperature and pressure. This led to modifications, from which evolved a single general law and a deeper insight into the molecular behavior of gases that was not possible until the exceptions had been understood. Yet, the new equations, the new laws, which encompassed the exceptions, in no way invalidated the operation of the original gas laws at room temperature. Likewise a consideration of the relationships between tumors in no way modifies the need for, or the criteria of every day hospital diagnosis. It may, however, give us added insight into the reasons for the behavior of each tumor. It also presents us with challenges to additional investigations that are not otherwise apparent: for example, if the field within which a tumor arises determines its cell type, speed of growth, and manner of spread, a proper understanding of the biologic laws which govern that field might lead to the means of control of the cells and eventually might permit conversion of bone tumors from more active to less active and even to manageable types.

This attempt at a general theory does not stand alone but is in keeping with the work in other classes of neoplasms. It is the essence of Bailey and Cushing's original work on gliomas and of Kernohan's more recent study, of Dr. Foot's studies of skin tumors here in New York, and of Friedman's and Moore's study of testicular tumors. Paradoxically, boundaries between individual tumors in each category become indistinct as our perception sharpens. One may reasonably hope that general theories of each major class of tumors may pave the way for a general theory of all neoplastic diseases.